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PRINADOL

Phenazocine (Prinadol - SKF) is a new analgesic-narcotic offered as a substitute for morphine. Like oxymorphone (Numorphan - Endo), which was discussed in the Oct. 28th issue of The Medical Letter, Prinadol is claimed to have greater analgesic activity than morphine, fewer undesirable side effects, and lower addictive liability.

Unlike oxymorphone, which is a close chemical relative of morphine, phenazocine, a substituted benzomorphan, retains only vestiges of its chemical relationship to the older drug. Nevertheless, a number of well-controlled studies show that it is as effective as morphine, with 1 mg. of Prinadol equivalent to about 4 mg. of morphine.

POTENCY AND SIDE EFFECTS - As with Numorphan, greater potency on a weight-for-weight basis does not make Prinadol more effective than morphine in relieving pain; and the claim that Prinadol in equivalent analgesic doses causes less respiratory depression, less hypotension, less sedation, and less nausea and vomiting than morphine has not been substantiated by controlled studies. The only definitive studies in the literature on the side effects of Prinadol are concerned with its respiratory depressant effects (J. W. Bellville, et al., Bull., Drug Addiction and Narcotics, Addendum, 3:28, 1960; and E. M. Greisheimer, et al., Anesthesiology, 21:370, 1960). These studies both indicate that Prinadol produces at least as much respiratory depression as comparable analgesic doses of other potent narcotics. (The claim that Prinadol has relatively little depressant effect has now been dropped.)

Like Numorphan, Prinadol is almost identical with morphine in peak, onset and duration of analgesic effect of equivalent doses (T. J. De Kornfeld and L. Lasagna, Anesthesiology, 21:159, 1960). The claim that in some cases Prinadol has relieved pain after other narcotic agents have failed may be correct, but it means nothing more than that patients vary in their preferences or responses to different drugs for unpredictable reasons. The same claim could as accurately be made for almost any narcotic.

On the basis of available evidence, Prinadol appears to be an acceptable analgesic for the management of severe pain, with only its newness and its high cost as deterrents to its use. The drug is available in ampules and multi-dose

vials in concentration of 2 mg. per cc. A 2-cc. (4-mg.) dose of Prinadol (in 10-cc. vials) costs about 30¢ as compared with 8¢ for a 15-mg. dose of morphine. Nalorphine (Nalline - Merck) and levallorphan (Lorfan - Roche) are effective antidotes for Prinadol.

MULTIVITAMIN SUPPLEMENTS

Teenamins (Rowell) is a new multivitamin preparation "especially formulated for the active, busy teenager, who is apt to neglect his or her diet." Myadec (Parke, Davis) is an older vitamin-mineral preparation now being promoted for "active people who won't take time to eat properly." There is nothing particularly noteworthy about either of these products, but both represent a large group of vitamin and vitamin-mineral preparations promoted to physicians with claims that foster certain false notions; for example, that such supplements are essential as nutritional "insurance" for healthy persons, or that they can safely be substituted for a balanced diet. The promotion copy for some products claims or implies that an excess of vitamins above normal requirements will relieve or prevent common infections, or degenerative or functional disorders.

DIETARY LACKS - Small amounts of all of the vitamins and of many minerals are essential to life, but there is no evidence that increasing the concentration of any vitamin or mineral above the normal level has any beneficial effect. An ordinary balanced diet supplies all the vitamins and other essential food factors except vitamin D and iodine. Exposure to sunlight probably provides adequate amounts of vitamin D for normal adults; it is desirable, however, to supplement the diets of children and pregnant and lactating mothers with 400 units a day of this vitamin; irradiated milk, viosterol and fish-liver-oil preparations are satisfactory sources. The use of iodized salt in regions where soil, food and water supply are deficient in iodine will take care of the body's iodine requirement.

Except for these additions, and in the absence of a diagnosed deficiency, the supplementation of a balanced diet with a vitamin or vitamin-mineral mixture has not been shown to "forestall infections," increase energy, diminish insomnia, improve well-being, or retard the aging process, as is claimed for one or another product. There is no convincing evidence that supplements of B_1 will improve the appetite of a child without a B_1 deficiency, or that supplements of B_{12} will accelerate growth in a child on an ordinary, balanced diet.

HARMFUL EFFECTS - Excessive amounts of vitamins A and D can cause harmful side effects. There is also potential danger in giving vitamin preparations containing folic acid to patients with undiagnosed anemia; this vitamin can mask pernicious anemia by alleviating the hematologic manifestations of the disease while allowing the neurologic complications to progress. Because of this hazard, the Food and Drug Administration has now limited to 0.4 mg. the amount of folic acid in a daily dose of a preparation sold without prescription.

Vitamin mixtures are among the most frequently given placebo "tonics," and they are usually quite safe. The administration of multivitamins, in lieu

of careful diagnostic studies, to patients complaining of fatigue, "nerves," and aches and pains is, however, to be condemned; the placebo effects of a vitamin product may for a time mask symptoms of serious organic disease. Multivitamin preparations should never be regarded as an adequate substitute for a balanced diet. No preparation has been - or in the present state of knowledge, can be - formulated which provides all of the essential nutritional factors found in food. As for the belief that large supplementary doses of vitamin C will prevent, abort or lessen the severity of colds and other respiratory infections, many controlled studies have failed to show any such effect.

CORTICOSTEROID THERAPY IN CHILDREN.

Systemic therapy with adrenal steroids is never without risk, and an awareness of the potential hazards is especially necessary in the treatment of infants and children. As with adults, severe bacterial infections, including septicemia, pneumonia, and staphylococcal and streptococcal infections, may complicate prolonged steroid therapy in children. Because of the anti-inflammatory effects of the steroids, moreover, an infection may reach an advanced stage before showing any overt sign.

It has been suggested that steroids given in large doses for brief periods after the onset of infection may be useful in some patients with serious acute infectious disease (W. W. Spink, Ann. Int. Med., 53: 1, 1960). This view is disputed, however; the efficacy of steroid therapy in overwhelming bacterial infections such as meningococcemia has not been supported by a lowered mortality rate in a significantly large series of cases (C. D. May, Pediatrics, 25: 316, 1960).

The hazards of steroid therapy in both adults and children with active or latent tuberculosis are well recognized. As a joint statement by the American Thoracic Society and the National Tuberculosis Association warns, "...the prolonged administration of corticosteroids is likely to exert a harmful effect upon the latency and course of tuberculosis..." When a patient with evidence of previous tuberculosis requires corticosteroid or ACTH treatment for more than two weeks, the statement advises the prophylactic administration of isoniazid (300 mg. daily for adults; 8 mg. per kg. for children).

VIRAL INFECTIONS - Controlled studies show that steroids reduce host resistance to viral infection (M. J. Romansky, JAMA, 170: 1179, 1959). The viral diseases of childhood may be unusually severe or prolonged in children receiving corticosteroids for other conditions. Chicken-pox, which normally is rarely fatal in children, has been reported as the cause of death in at least 12 children receiving steroids (W. D. Nichols, Am. J. Dis. Children, 94: 219, 1957). Long-term steroid therapy should not be started, therefore, at a time when a susceptible child has been exposed to a contagious disease. If a child already on regular steroid therapy is exposed, dosage should, if possible, be reduced to physiological levels, that is, to not more than 5 mg. of prednisone or its equivalent daily, in divided doses. On the other hand, when infection occurs in a patient receiving physiologic doses of steroids for adrenal or pituitary insufficiency or adrenogenital syndrome, dosage must be maintained or even increased.

EFFECT ON GROWTH - Growth suppression is another hazard of prolonged steroid therapy (F. M. Blodgett, et al., N. E. J. Med., 254:636, 1956), though a spurt in growth occurs when therapy is stopped. When corticosteroids are used in children, therapy should, if possible, be intermittent rather than continuous. The effect on growth is not, of course, a serious contraindication to the use of steroids in nephrosis or leukemia. In less serious cases, the risk of growth suppression and other side effects must be weighed against the benefits of therapy.

In animals, corticosteroid therapy during pregnancy may produce abortion and congenital defects in the offspring. A few clinical reports have suggested the possibility of such occurrence in humans, but the connection has not been definitely established. In addition to the usual side effects of steroids in both adults and children, a pseudo brain-tumor syndrome (headache, papilledema and oculomotor paralysis) has been reported in children. It disappears promptly, however, if the syndrome is recognized and therapy discontinued.

MEPROBAMATE TOXICITY

"Medical Letter consultants do not find convincing evidence that meprobamate affords any distinct advantage over appropriate doses of the barbiturates either as a hypnotic or as a daytime sedative for the relief of neurotic anxiety and tension." This statement appeared in an appraisal of meprobamate (Miltown - Wallace; Equanil - Wyeth) in the October 28th issue of The Medical Letter, and it was quoted by the New York Herald Tribune a few days later in a news item on the Medical Letter appraisal. Subsequently, the correspondence columns of the Herald Tribune carried a letter from a New York psychiatrist claiming that meprobamate is "better for humanity" than the barbiturates if for no other reason than that "... those who take meprobamate with suicidal intent do not succeed in this intent." The same belief that overdoses of meprobamate cannot cause death has been expressed by other physicians in letters to The Medical Letter.

Since such belief may encourage the prescription of meprobamate for patients with known or suspected suicidal tendencies, the record needs to be set straight. E. M. Caffey, Jr., et al., writing in the Medical Bulletin of the Veterans Administration (Sept. 12, 1960) point out that "Meprobamate overdosage may be fatal, sometimes from as little as 16 gm. of the drug. The hazards are similar to those from barbiturate overdosage, including hypotension and respiratory depression.... Like barbiturates, meprobamate may have a synergistic effect with alcohol which has played a role in many of the reported fatalities."

The medical literature records at least four suicides with meprobamate, and the actual number is doubtless far greater. Thus, in the city of Philadelphia alone, over the past four years, eight suicides with meprobamate have been documented by investigation and toxicologic analysis. Discussion with officials who keep mortality records discloses the belief that some deaths from overdoses of meprobamate and other non-barbiturate sedatives and hypnotics are attributed in death certificates to "barbiturates," as a sort of catch-all term for sedative drugs. In small doses, properly used, meprobamate is a relatively safe sedative drug, but it would be hazardous for physicians to overlook its lethal potential.

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